Sleep Medicine 15 (2014) 1055–1061

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Neurocognitive dysfunction and grey matter density deficit in children with obstructive sleep apnoea

KC Chan [a,*], L Shi [b], HK So [a], D Wang [b], AWC Liew [c], DD Rasalkar [b], CW Chu [b], YK Wing [d], AM Li [a]

[a] Department of Paediatrics, The Chinese University of Hong Kong, Shatin, Hong Kong
[b] Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Shatin, Hong Kong
[c] School of Information and Communication Technology, Griffith University, Gold Coast Campus, Queensland, Qld 4222, Australia
[d] Department of Psychiatry, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong

ARTICLE INFO

Article history:
Received 25 January 2014
Received in revised form 31 March 2014
Accepted 2 April 2014
Available online 6 June 2014

Keywords:
Obstructive sleep apnoea
Paediatric
Child
Cognitive function
Grey matter density
Brain
Magnetic resonance
Voxel-based morphometry

ABSTRACT

Background: Cerebral structural changes related to obstructive sleep apnoea (OSA) have been reported in adult OSA patients; however, similar data and their associations with neurocognitive dysfunction are scarce in childhood OSA.
Objective: To compare neurocognitive function, regional grey matter density and cerebral volume in children with and without OSA.
Methods: Fifty OSA cases and 27 normal controls underwent a panel of neurocognitive tests. High resolution 3-dimensional magnetic resonance images of the brain were obtained from 23 OSA cases and 15 gender and age matched controls. Total cerebral volume and regional grey matter density were analyzed using voxel-based morphometry technique and compared between the two groups. Individuals with an obstructive apnoea hypopnoea index (OAHI) > 5 were defined as having moderate-to-severe OSA.
Results: Children with OSA showed significantly reduced attention and visual-fine motor coordination scores compared with controls. Grey matter volume deficit was observed in prefrontal and temporal regions of cases with moderate-to-severe OSA only. Significant negative correlations were found between the visual-fine motor coordination score and the ratio of grey matter volume over total brain volume.
Conclusion: Children with OSA had impaired attention and visual-fine motor coordination. Regional grey matter reduction was evident in children with more severe OSA.

1. Introduction

Childhood obstructive sleep apnoea (OSA) is a common sleep disorder, affecting around 5% of school-aged children [1]. The condition is characterised by prolonged partial and/or intermittent complete upper airway obstruction. Repeated apnoeas and hypopnoeas during sleep result in intermittent gaseous exchange abnormalities, cortical and sympathetic nervous system arousals, and sleep fragmentation [2]. If untreated it can lead to neurocognitive, cardiovascular morbidities and increased health care expenditure [2,3].

Sleep is important in the consolidation and integration of memory, which is an integral part of the learning process [4]. A number of reviews have consistently demonstrated impairments in attention, memory and learning, verbal skills, general intelligence, behavioural and emotional control in children with OSA [5–7]. Though the underlying pathogenesis remains undefined, cerebral structural changes related to OSA have been suggested and grey matter loss has been reported in adult OSA patients. Voxel-based morphometry studies have documented grey matter density attenuation in frontal, parietal, temporal, hippocampal and cerebellar regions of adult patients with OSA [8–12]. However, inconsistent findings as a result of methodological and sampling variability are also evident [13]. None of the reported studies were carried out in children, and the relationship between structural changes and neurocognitive function is also unknown. A longitudinal neuroimaging study demonstrated that changes in cortical grey matter were nonlinear and regionally specific in childhood and adolescents. There was a pre-adolescent increase followed by a post-adolescent decrease, with developmental peaking at different ages for different areas of the brain [14]. Histological animal studies showed massive synaptic proliferation in the prefrontal area in early

* Corresponding author at: Dr Kate C.C. Chan, Department of Paediatrics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong. Tel.: +852 26322840; fax: +852 26360020.
E-mail address: katechan@cuhk.edu.hk (K.C. Chan).

http://dx.doi.org/10.1016/j.sleep.2014.04.011
1389-9457/

adolescence, followed by a plateau, reduction, and then reorganisation phase. These findings were supported by neuroimaging studies [15–17]. Massive synaptic proliferation and subsequent reduction and reorganisation at the periadolescent period may represent a critical stage of neurodevelopment. As prefrontal areas are linked to neurocognition like executive functioning, the influence of sleep disordered breathing may affect the brain and thus neurobehavioural development.

This current study aimed to investigate neurocognitive function, global cerebral and grey matter volume in children with OSA and compared with age and gender matched normal subjects. We hypothesised that neurocognitive dysfunction and structural brain changes could be demonstrated in children with OSA.

2. Methods

2.1. Subjects

Children aged between 8 and 13 years were recruited from 13 randomly selected schools. Parents of these school children completed a validated screening questionnaire that stratified children into high or low risk for OSA [18]. Children were excluded from the study if they had illness within 4 weeks of PSG, suffered from cardiac, renal and neuromuscular diseases, had physician diagnosed attention deficit hyperactivity disorder, had chromosomal abnormalities or had undergone upper airway surgery. All children at high risk for OSA and a randomly selected sample from the low risk group were invited to undergo overnight polysomnography (PSG) at a dedicated sleep laboratory with CNS 1000P polygraph (CNS, Inc., Chanhassen MN) [19]. Details of PSG and definition of various OSA parameters have been reported in our previous publications [1,20,21]. All computerised sleep data were further manually edited by experienced polysomnography technologists and clinicians according to standardised criteria [22,23]. An obstructive apnoea was defined as the absence of airflow with persistent respiratory effort lasting longer than two baseline breaths, irrespective of arterial oxygen saturation changes. An obstructive hypopnoea was defined as a reduction of 50% or more in the amplitude of the airflow signal with persistent respiratory effort. It was only quantified if it was longer than two baseline breaths and was associated with oxygen desaturation of at least 3% and/or arousals. The obstructive apnoea hypopnoea index (OAHI) was defined as the total number of obstructive apnoeas and obstructive hypopnoeas per hour of total sleep time.

Subjects were classified as: healthy control group (obstructive apnoea hypopnoea index (OAHI) < 1 and history of snoring <3 nights per week), mild OSA (OAHI 1 to 5), and moderate-to-severe OSA (OAHI ≥ 5). Subjects with primary snoring (OAHI < 1 and history of snoring 3 nights or more per week) were not included as there was a potential of misclassifying subjects with upper airway resistance syndrome (UARS) as primary snoring. This current study therefore concentrated on comparing subjects with OSA with normal controls. The diagnostic criteria for childhood OSA has not been well established in children and the clinical importance of any particular cutoff is still undetermined [24]. In our study, childhood OSA was defined by using OAHI ≥ 1 which is widely used to describe childhood OSA [25]. In our experiences, OAHI ≥ 5 correlated best with cardiovascular outcome in cross-sectional studies. Therefore, children with OAHI ≥ 5 were defined as moderate-to-severe OSA [20,21].

The first 50 children diagnosed to have OSA and 30 controls were invited to have neurocognitive function assessment. As a result of financial limitation, only a subgroup of the recruited subjects and controls underwent MRI brain imaging. The following information was also captured in the OSA questionnaire: gestation at birth, tobacco smoke exposure, average sleep duration during a typical week, weekdays and weekends, living conditions, family income and parental educational status [26]. This study was approved by Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (Reference number: 2004.144). Informed written consent and assent were obtained from parents and subjects, respectively.

2.2. Neurocognitive function assessment

Neurocognitive function was assessed using Hong Kong List Learning Test (HKLLT) R1-5 and B1-6; Trail Making Test (TMT) A and B; Grooved Pegboard Test and Wechsler's Intelligence Scale for Children in Hong Kong (HK-WISC). All assessments were carried out by a registered clinical psychologist who was blinded to the PSG results of the subjects.

HKLLT is a Chinese language-based learning test to assess learning abilities and verbal memory. A higher score indicates better performance [27]. TMT is a validated tool for assessment of attention, speed of processing, mental flexibility and executive functions. It consists of two parts. Part A requires the subject to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. Part B is similar except the subject needs to alternate between numbers and letters. Part A primarily examines cognitive processing speed and part B examines executive functioning [28,29]. Grooved Pegboard Test assesses visual-fine motor coordination. It is a manipulative dexterity test consisting of 25 holes with randomly positioned slots. Pegs with a key along one side must be rotated to match the hole before they can be inserted. The dominant hand trial is administered first and followed by the non-dominant hand [30,31]. In both TMT and Grooved Pegboard Test, a child performs better if a shorter time is needed to finish the test. HK-WISC is a locally validated intelligent quotient (IQ) assessment for children containing a panel of psychological subtests to measure a child's IQ with standardised procedures. A higher score signifies a better performance [32,33].

2.3. MR protocol

The children were examined in a 1.5-T MR imager (Sonata, Siemens, Erlanger, Germany) using a standard head coil. A magnetisation prepared rapid acquisition gradient echo (MPRAGE) sequence was used with the following parameters: (Repetition time [TR] = 2070 msec; echo time [TE] = 3.93 msec; time of inversion [TI] = 1110 msec; Flip angle = 15; FOV 230 mm, Slice thickness 0.9 mm, no gap, Resolution 256 × 256). High resolution iso-voxel brain images were obtained (total 192 slides) with the scanning time of around 8 minutes for each subject. All MR examinations were reviewed by two radiologists blinded to the PSG results and the results were determined by mutual agreement.

2.4. Voxel-based morphometry (VBM)

The quality of all acquired dataset was visually checked to exclude any motion artefacts before detailed analysis. VBM is an unbiased whole-brain technique for characterising regional cerebral volume and tissue concentration differences in structural magnetic resonance images [34]. The optimised VBM approach is an improved version of the standard VBM which has been demonstrated to achieve better segmentation results [35]. Images were spatially normalised and segmented into grey matter, white matter and cerebrospinal fluid. After segmentation and smoothing, statistical analysis was performed to make inferences about group differences. For each tissue type, the statistical t-test was applied to generate a parametric map showing regions where tissue concentration differed significantly. The technique has been widely used in identifying changes in local concentration of grey matter in patients with various diseases [36].

Table 1
Characteristics of subjects and controls who had undergone neurocognitive function tests.

	Non-OSA ($n = 27$)	OSA ($n = 50$)	*P*-value
Age (years)	10.9 (9.4–12.1)	10.4 (8.8–11.9)	0.47
Gender (M/F)	19/8	37/13	0.73
OAHI	0.0 (0.0–0.1)	3.0 (2.0–6.8)	<0.0001
Body height (cm)	131.0 (124.5–143.0)	134.0 (123.9–144.3)	0.94
Body weight (kg)	29.2 (25.8–40.7)	32.20 (26.1–40.3)	0.70
BMI (kg/m^2)	17.60 (15.5–19.2)	17.8 (16.0–20.6)	0.77
BMI z-score [42]	0.5 (−0.3 to 0.9)	0.5 (−0.3 to 1.4)	0.85
Average sleep duration			
Over 7 days (h)	9.0 (8.6–9.5)	9.1 (8.6–9.8)	0.54
Weekdays (h)	9.0 (8.3–9.3)	9.0 (8.2–9.8)	0.74
Weekends (h)	9.5 (9.0–10.5)	9.8 (9.5–10.5)	0.55
Full-term delivery	94.0%	88.9%	0.43
Family members smoke at home	26.0%	25.9%	0.99
Housing			0.78
Private	56.0%	59.3%	
Public	44.0%	40.7%	
Living area (sq. ft)			0.87
≤400	20.0%	18.5%	
400–600	38.0%	33.3%	
≥600	42.0%	48.2%	
Family income (HKD, monthly)			0.34
<15,000	37.0%	26.5%	
≥15,000	63.0%	73.5%	
Father's education (secondary or above)	88.9%	89.8%	0.14
Mother's education (secondary or above)	76.9%	77.6%	0.95

OSA, obstructive sleep apnoea; OAHI, obstructive sleep apnoea–hypopnoea index; BMI, body mass index; HKD, Hong Kong dollars.
Values are median (interquartile range) or percentage.

2.5. Total cerebral analysis

The volumes of grey matter and white matter were computed from the modulated, segmented images of the supratentorial region. Total cerebral grey matter volumes and grey-to-white matter ratio were compared between the control group and each of the two patient groups using independent two-tailed t-test assuming equal variance with a threshold of $\alpha = 0.05$.

2.6. Regional volume analysis

Regional volume analysis was performed using Matlab and SPM5 (The Wellcome Trust Centre for Neuroimaging, University College London, UK). The optimised VBM approach was employed to analyse the acquired MR brain images [35]. Due to the non-linear transformation of the spatial normalisation step, the volumes of certain brain regions might grow or shrink. To preserve the volume of a particular tissue within a voxel, a modulation process for correcting volume changes was applied to the segmented tissue images. The brainstem and cerebellum were excluded from analysis in this study due to frequent artefacts at the above regions in the MR images. A mask was created by manual delineation and then applied to the modulated images to obtain the supratentorial region for subsequent analysis.

The segmented images were smoothed with a 12-mm FWHM filter and then analysed using statistical parametric mapping (SPM5). Regional differences in grey matter between patients and controls groups were assessed at significance level of $p < 0.001$.

2.7. Statistical analysis

The subjects were divided into two groups (non-OSA: OAHI ≤ 1, OSA: OAHI > 1), according to their OAHI score. For neurocognitive tests, the primary predictor variable was group status (non-OSA versus OSA). Secondary predictor variables were grey matter volume, grey-to-white matter ratio, total brain volume and grey-to-total brain ratio. Primary outcomes were mean standard neurocognitive test scores. Levene's test was used to ensure homogeneity of variance between groups. The demographic data and neurocognitive outcomes were expressed as median with interquartile ranges (IQR) as the distribution of the results were non-parametric. The Mann–Whitney U test for the quantitative variables and chi-square test for the categorical variables were used to explore the associations of the factors between these two groups. Relationship between neurocognitive function test performance and the ratio of grey matter volume over total brain volume was analysed with Spearman correlations. All the statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided and P-value <0.05 was considered statistically significant.

3. Results

Three control subjects declined to participate in this study; thus 50 OSA and 27 non-OSA children (mean age: 10.5 ± 1.9, 56 boys) were included for final analysis. There were no statistically significant differences in baseline demographics and characteristics between the two groups except for OAHI (Table 1). Children with OSA had significantly higher OAHI, arousal index and proportion of stage 1 sleep than the control group (Table 2). The differences could be explained by more cortical arousals following apnoeas or hypopnoeas in children with OSA. Otherwise, the sleep time, sleep efficiency and sleep architectures were comparable between the two groups.

3.1. Neurocognitive function assessment

Children without OSA performed significantly better than children with OSA in Trail Making Test [Part A: 40s (31–49 s)] in non OSA group vs. 47s [(35.2–53.3 s) in OSA group; p = 0.036] and Grooved Pegboard Test [dominant 5 rows: 67 s (59.8–73.8 s)] in non OSA group vs. 74 s (65.8–83.3 s) in OSA group; p = 0.02 and non-dominant 5 rows: 70.98s (68–76.5 s) in non OSA group vs. 79s [(73.4–93.3 s) in OSA group; p = 0.002] (Table 3). This suggested that children with OSA had reduced attention and visual-fine motor coordination compared with children without OSA. No significant differences were identified between the two groups in other neurocognitive tests.

Table 2
Sleep parameters in subjects and controls.

	Non-OSA ($n = 27$)	OSA ($n = 50$)	*P*-value
OAHI (/h)	0.0 (0.0–0.1)	3.0 (1.9–6.8)	<0.001
ODI	0.0 (0.0–0.1)	1.0 (0.2–2.4)	<0.001
Arousal index (/h)	5.6 (3.0–7.3)	7.9 (5.4–10.1)	0.003
Oxygen nadir (%)	94 (92–95)	91 (89–93)	<0.001
Actual sleep time (min)	470 (412–507)	466 (436–509)	0.902
Sleep efficiency (%)	83.9 (74.9–88.7)	82.0 (72.9–88.6)	1.000
Stage 1 (%)	5.4 (4.1–7.1)	8.8 (6.3–11.3)	<0.001
Stage 2 (%)	48.8 (42.0–54.6)	48.8 (46.3–52.2)	0.717
Stage 3 (%)	6.8 (5.3–9.2)	6.9 (5.3–9.0)	0.983
Stage 4 (%)	16.8 (13.5–20.9)	15.7 (11.6–19.8)	0.175
REM (%)	20.4 (17.1–23.6)	19.9 (16.6–23.1)	0.474

OSA, obstructive sleep apnoea; OAHI, obstructive sleep apnoea–hypopnoea index; ODI, oxygen desaturation index; REM, rapid eye movement sleep.
Values are median (interquartile range).

3.2. MR voxel-based morphometry

Twenty-three OSA subjects (mean age: 10.51 ± 1.88) of whom 15 had mild OSA and the remaining with more severe disease underwent MRI brain imaging. All subjects were right-handed and were neurologically normal on clinical examination. None of the subjects had significant intracerebral abnormalities. Subjects who underwent MRI and those who were not invited were similar in demographic and PSG data, sleep duration, socio-economic status and parental education except for body weight, body mass index (BMI) and BMI z-score. Subjects who had MRI were significantly heavier than those who did not [body weight (kg): 34 (28.5–43.4) in MRI group vs. 29 (23.4–36.35) in non-MRI group; $p = 0.03$; BMI (kg/m2): 18.6 (17.1–22.2) in MRI group vs. 17.1 (15.0–19.2) in non-MRI group; $p = 0.01$; BMI z-score: 0.7 (0.2–1.7) in MRI group vs. 0.4 (–0.36–0.9) in non-MRI group; $p = 0.01$]. However, for the 23 subjects and 15 controls who had cranial MRI, no significant differences could be found in any of the above parameters.

3.3. Total cerebral grey-white matter analysis

At a threshold level of $\alpha = 0.05$, no significant difference was observed between the subjects and the controls (Table 4).

3.4. Regional analysis

When assessed at a threshold of $p < 0.001$ and a minimum cluster size of 20, seven clusters of grey matter deficits were observed only in subjects with moderate-to-severe OSA when compared with the control group (Fig. 1).

Figure 1 shows the maximum intensity projection (MIP) of the statistical map projected on a normalised glass brain in three orthogonal planes. Areas of grey matter deficits included the left and right superior frontal gyri, right supramarginal gyrus, left lateral occipital gyrus and left superior temporal gyrus whereas no significant increase was detected. No significant grey matter change was observed in patients with mild OSA.

Significant negative correlations were found between the Grooved Pegboard test and the ratio of grey matter volume over total brain volume ($r = –0.463$ and $–0.520$ for dominant 5 rows and non-dominant 5 rows tests, respectively, $p < 0.05$), i.e. the lower the grey matter volume, the longer the time the child needed to finish the test and hence poorer the performance.

4. Discussion

To our knowledge, this is the first study investigating the relationship between neurocognitive dysfunction and MRI brain structural changes in children with OSA. We demonstrated that when compared with controls, children with OSA showed reduced attention and visual motor coordination. Subjects with more severe OSA were found to have regional grey matter deficits, and the degree of which had a significant negative correlation with visual motor coordination score.

Grey matter deficits were noted in seven local areas, which could be classified into three main anatomical regions: (1) bilateral superior frontal gyri which are part of the prefrontal cortex and left superior temporal gyrus which is within the limbic system; (2) right supramarginal gyrus within the somatosensory cortex; and (3) left lateral occipital gyrus which is closely related to the visual cortex. Some of these regions are in close proximity to areas of grey matter deficits reported in adults with OSA and near to the water-shed area of vascular supply [8–10]. The overall picture suggests that there are certain brain regions which are more susceptible to OSA insult

Table 3
Neuropsychological test results between subjects and controls.

	Non OSA ($n = 27$)	OSA ($n = 50$)	*P*-value
Trail Making Test			
Part A (s)	40.0 (31.0–49.0)	47.0 (35.2–53.3)	0.04
Part B (s)	89.0 (66.0–141.0)	94.0 (70.2–128.0)	0.69
Grooved Pegboard Test			
Dominant five rows (s)	67.00 (59.80–73.8)	74.0 (65.8–83.3)	0.02
Non-dominant five rows (s)	71.0 (68.0–76.5)	79.0 (73.4–93.3)	0.002

OSA, obstructive sleep apnoea.
Values are median (interquartile range).

Table 4
Comparison between subjects and controls on total and regional brain volume and density.

Brain volume and density	All cases: OAHI ≥ 1	OAHI = 1–5	OAHI ≥ 5	Control
	($n = 23$)	($n = 15$)	($n = 8$)	($n = 15$)
Grey matter volume (cm^3)	700.3 (656.8–721.0)	689.2 (654.6–715.9)	718.7 (674.1–738.9)	668.3 (621.9–710.6)
Grey/white matter ratio	1.89 (1.73–2.04)	1.84 (1.68–2.00)	1.93 (1.82–2.05)	1.83 (1.75–1.89)
Total brain volume (cm^3)	1333.4 (1242.8–1405.0)	1327.4 (1218.8–1390.2)	1352.8 (1275.2–1427.8)	1282.9 (1193.0–1410.6)
Grey/total brain ratio	0.52 (0.51–0.53)	0.52 (0.51–0.53)	0.52 (0.51–0.53)	0.52 (0.51–0.54)

OAHI, obstructive sleep apnoea–hypopnoea index.
Values are median (interquartile range).
No significant differences were found.

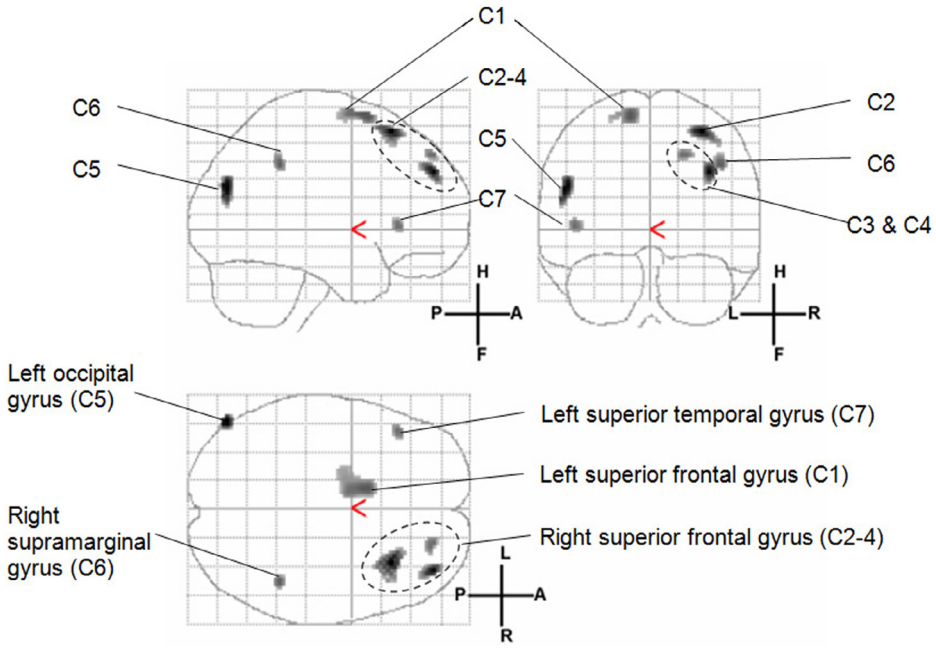

Fig. 1. Maximum intensity projection (MIP) of the statistical map showing areas of grey matter deficits in patients with moderate-to-severe obstructive sleep apnoea. The MIP is projected on a glass brain in three orthogonal planes. Corresponding brain regions: C1, left superior frontal gyrus; C2–4, right superior frontal gyrus; C5, left occipital gyrus; C6, right supramarginal gyrus; C7, left superior temporal gyrus.

than others. Reduction in grey matter volume in OSA subjects may be explained by the effect of repeated apnoeas and hypoxic damage to the brain. Beebe and Gozal proposed that sleep fragmentation and physiological changes related to OSA caused prefrontal cortex (PFC) dysfunction, which led to the cognitive and behavioural deficits seen in children with OSA [37]. The prefrontal cortex is involved in attention and executive functions. It shows decreased activity during all sleep stages which may serve as a mechanism to maintain its function. It also appears more vulnerable to the physiological sequelae of OSA because of its relatively late maturity compared with other brain regions [37,38]. On the other hand, lateral occipital gyrus is closely related to the visual cortex. Grey matter deficits in these areas might explain the impaired attention and visual-motor coordination demonstrated in our subjects.

Our study was the first MR morphometric brain study on children with OSA, comparing a homogeneous group of OSA children with narrow age range with age and sex-matched controls. There was far less regional grey matter deficit in our cohort when compared with the reported adult series [8,10]. This is not unexpected, as our subjects were much younger, with shorter duration of illness and exposure to the detrimental effects from OSA compared with adults. Though the changes were less extensive, unlike in the adult cohort where cerebral volume change might be affected by normal aging or presence of co-morbidity, the changes observed in our paediatric subjects should be considered more likely a sequelae of OSA.

The major limitation of this study was the small sample size. MR morphometric brain study was carried out in only 38 children who had undergone neurocognitive function assessment. Though grey matter deficit was demonstrated in the more severe OSA subjects as a group, its association with neurocognitive impairment and the individual susceptibility to end-organ injury by OSA were not clearly reflected. The small number of moderate-severe OSA subjects is another limitation of this cohort; however, this is an intrinsic factor that few children suffer from more severe OSA. To avoid possible influence on the statistical results, we have adopted the threshold for uncorrected p-value <0.001, which is a rather stringent criterion. Similar sample size and p-value threshold have also been described in other published VBM studies [39]. Another limitation was that children who received MRI had higher body weight, BMI and BMI z-score than those who did not. Some adult studies reported that global brain volume and regional grey matter volume were negatively correlated with BMI [40,41]. However, this correlation is not well established in paediatric age group. Moreover, there was no significant difference in terms of body weight, BMI and BMI z-score between the OSA and control groups who had MRI. The effect of body weight and BMI on the overall interpretation of MR VBM result should therefore be minimal. Being a cross-sectional study, we could not assess whether these neurocognitive impairment and grey matter deficits are reversible with treatment. Although the grey matter changes were less extensive in our patient group when compared with adults, whether children's developing brain is more prone to the physiological sequalae of OSA remains a major question. A follow up study would be valuable to look for any interval change of the structural brain abnormalities and neurocognitive dysfunction of this cohort of patients with OSA.

In conclusion, the findings of this study suggested that regional grey matter reduction is present in a cohort of young subjects with more severe OSA. Children with OSA were demonstrated to have impaired attention and visual motor coordination. The grey matter deficits might be related to neurocognitive deficit reported. Childhood OSA might alter a developing brain's neurocognitive potential; therefore, it is important to identify and provide treatment to children with OSA promptly.

Financial/nonfinancial disclosures

Dr Wing has received honorarium by serving as a part-time paid consultant for the Renascence Therapeutics. All other authors have no potential conflicts of interest exist with any companies/

organisations whose products or services may be discussed in this article.

Funding sources

The study was supported by: Direct Grant for Research 4450162, The Chinese University of Hong Kong.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.04.011.

Acknowledgement

Author contributions: Dr Chan is the guarantor of the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Chan: contributed to the project planning, recruitment of subjects, revision of the article, and approval of the final manuscript.

Dr Shi: contributed to the data analysis, revision of the article, and approval of the final manuscript.

Dr So: contributed to the data analysis, revision of the article, and approval of the final manuscript.

Dr Wang: contributed to the data analysis, revision of the article, and approval of the final manuscript.

Dr Liew: contributed to the data analysis, revision of the article, and approval of the final manuscript.

Dr Rasalkar: contributed to the radiological examination and interpretation, revision of the article, and approval of the final manuscript.

Dr Chu: contributed to the radiological examination and interpretation, data analysis, revision of the article, and approval of the final manuscript.

Dr Wing: contributed to the revision of the article and approval of the final manuscript.

Dr Li: contributed to the project planning, recruitment of subjects, revision of the article and approval of the final manuscript.

We thank Yin-Heung P Ng (PhD) for her help in the initial voxel based morphometry analysis.

Role of sponsors: Unrestricted funding was provided by the CUHK Direct Grant for Research. The design, execution, data collection and analysis of the study were carried out solely by the research team without involvement of the funding body.

Other contributions: This work was performed at the Department of Pediatrics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong. We are grateful for the cooperation and participation of all the children and their parents.

References

[1] Li AM, So HK, Au CT, et al. Epidemiology of obstructive sleep apnoea syndrome in Chinese children: a two-phase community study. Thorax 2010;65(11):991–7.
[2] Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2012;130(3):576–84.
[3] Tarasiuk A, Greenberg-Dotan S, Simon-Tuval T, et al. Elevated morbidity and health care use in children with obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2007;175(1):55–61.
[4] Stickgold R. Sleep-dependent memory consolidation. Nature 2005;437(7063):1272–8.
[5] Beebe DW. Neurobehavioral morbidity associated with disordered breathing during sleep in children: a comprehensive review. Sleep 2006;29(9):1115–34.
[6] Kohler MJ, Lushington K, Kennedy JD. Neurocognitive performance and behavior before and after treatment for sleep-disordered breathing in children. Nat Sci Sleep 2010;2:159–85.
[7] Owens JA. Neurocognitive and behavioral impact of sleep disordered breathing in children. Pediatr Pulmonol 2009;44(5):417–22.
[8] Macey PM, Henderson LA, Macey KE, et al. Brain morphology associated with obstructive sleep apnea. Am J Respir Crit Care Med 2002;166(10):1382–7.
[9] Morrell MJ, McRobbie DW, Quest RA, Cummin AR, Ghiassi R, Corfield DR. Changes in brain morphology associated with obstructive sleep apnea. Sleep Med 2003;4(5):451–4.
[10] Joo EY, Tae WS, Lee MJ, et al. Reduced brain gray matter concentration in patients with obstructive sleep apnea syndrome. Sleep 2010;33(2):235–41.
[11] Canessa N, Castronovo V, Cappa SF, et al. Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. Am J Respir Crit Care Med 2011;183(10):1419–26.
[12] Yaouhi K, Bertran F, Clochon P, et al. A combined neuropsychological and brain imaging study of obstructive sleep apnea. J Sleep Res 2009;18(1):36–48.
[13] O'Donoghue FJ, Briellmann RS, Rochford PD, et al. Cerebral structural changes in severe obstructive sleep apnea. Am J Respir Crit Care Med 2005;171(10):1185–90.
[14] Giedd JN, Blumenthal J, Jeffries NO, et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci 1999;2(10):861–3.
[15] Colver A, Longwell S. New understanding of adolescent brain development: relevance to transitional healthcare for young people with long term conditions. Arch Dis Child 2013;98(11):902–7.
[16] Giedd JN. The teen brain: insights from neuroimaging. J Adolesc Health 2008;42(4):335–43.
[17] Casey BJ, Trainor RJ, Orendi JL, et al. A developmental functional MRI study of prefrontal activation during performance of a Go–No-Go task. J Cogn Neurosci 1997;9(6):835–47.
[18] Li AM, Cheung A, Chan D, et al. Validation of a questionnaire instrument for prediction of obstructive sleep apnea in Hong Kong Chinese children. Pediatr Pulmonol 2006;41(12):1153–60.
[19] Li AM, Wing YK, Cheung A, et al. Is a 2-night polysomnographic study necessary in childhood sleep-related disordered breathing? Chest 2004;126(5):1467–72.
[20] Li AM, Au CT, Sung RY, et al. Ambulatory blood pressure in children with obstructive sleep apnoea: a community based study. Thorax 2008;63(9):803–9.
[21] Chan JY, Li AM, Au CT, et al. Cardiac remodeling and dysfunction in children with obstructive sleep apnoea: a community based study. Thorax 2009;64(3):233–9.
[22] American Thoracic Society. Cardiorespiratory sleep studies in children: establishment of normative data and polysomnographic predictors of morbidity. Am J Respir Crit Care Med 1999;160(4):1381–7.
[23] American Academy of Sleep Medicine. International classification of sleep disorders, diagnostic and coding manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005. p. 56–9.
[24] Marcus CL. Childhood obstructive sleep apnea syndrome: unanswered questions. Chest 2008;134(6):1114–15.
[25] Carroll JL. Obstructive sleep-disordered breathing in children: new controversies, new directions. Clin Chest Med 2003;24(2):261–82.
[26] Wing YK, Li SX, Li AM, Zhang J, Kong AP. The effect of weekend and holiday sleep compensation on childhood overweight and obesity. Pediatrics 2009;124(5):e994–1000.
[27] Chan A, Kwok I. Hong Kong List Learning Test (HKLTT): manual and preliminary norms. Hong Kong: Department of Psychology, The Chinese University of Hong Kong; 1998.
[28] Tombaugh TN. Trail making test A and B: normative data stratified by age and education. Arch Clin Neuropsychol 2004;19(2):203–14.
[29] Bowie CR, Harvey PD. Administration and interpretation of the trail making test. Nat Protoc 2006;1(5):2277–81.
[30] Lafayette Instruments. Grooved pegboard test user's manual. Lafayette: Lafayette Instruments; 2002.
[31] Bornstein RA. Normative data on selected neuropsychological measures from a nonclinical sample. J Clin Psychol 1985;41(5):651–9.
[32] Wechsler D. The Wechsler intelligence scale for children fourth edition. London: Pearson Assessment; 2004.
[33] Psychological Corporation. Hong Kong Wechsler intelligence scale for children manual. New York: Psychological Corporation; 1981.
[34] Ashburner J, Friston KJ. Voxel-based morphometry – the methods. Neuroimage 2000;11(6 Pt 1):805–21.
[35] Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14(1 Pt 1):21–36.
[36] Beyer MK, Janvin CC, Larsen JP, Aarsland D. A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry. J Neurol Neurosurg Psychiatry 2007;78(3):254–9.
[37] Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res 2002;11(1):1–16.
[38] Kennedy JD, Blunden S, Hirte C, et al. Reduced neurocognition in children who snore. Pediatr Pulmonol 2004;37(4):330–7.

[39] Whitwell JL, Sampson EL, Loy CT, et al. VBM signatures of abnormal eating behaviours in frontotemporal lobar degeneration. Neuroimage 2007;35(1):207–13.
[40] Taki Y, Kinomura S, Sato K, et al. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. Obesity 2008;16(1):119–24.
[41] Ward MA, Carlsson CM, Trivedi MA, Sager MA, Johnson SC. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. BMC Neurol 2005;5:23.
[42] Leung SS, Cole TJ, Tse LY, Lau JT. Body mass index reference curves for Chinese children. Ann Hum Biol 1998;25(2):169–74.